

TRANSIENT PATTERN FORMATION IN A STOCHASTIC MODEL OF CANCER GROWTH

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(Dated: 13 May 2005)

Abstract

We study a spatially inhomogeneous model of cancer growth based on Michaelis–Menten kinetics, subjected to additive Gaussian noise and multiplicative dichotomous noise. In presence of the latter, we can observe a transition between two stationary states of the system, The transient behaviour generates a spatial pattern of two phases, where cancer cells or immune cells predominate.

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I. INTRODUCTION

The presence of noise in biological systems may be regarded not only as a mere source of disorder but also as a factor which introduces positive and organising rather than disruptive changes in the system's dynamics. Some of the more important examples of noise induced effects are: stochastic resonance [1], resonant activation [2, 3, 4], noise enhanced stability [5], stochastic hysteresis and synchronisation [6, 7], bifurcation effects [8] or pattern formation [9, 10].

The effect of cell-mediated immune surveillance against cancer [11, 12, 13] may be a specific illustration of the coupling between noise and a biological system. The series of reactions between cytotoxic cells and a tumour tissue may be considered to be well approximated [11] by a saturating, enzymatic-like process whose time evolution equations are similar to the standard Michaelis–Menten kinetics. Random variability of kinetic parameters defining that process may affect the extinction of the tumour [11, 14]. In the present paper, we investigate the effect of pattern formation in a spatially inhomogeneous model of cancer growth. We describe the dynamics of the system in terms of chemical reactions.

Biochemical reactions are usually described in terms of phenomenological kinetic rates formulated by standard stoichiometric analysis. In such deterministic models, molecular fluctuations can be incorporated by including additional source of stochastic fluxes represented e.g. by the additive white noise:

$$\frac{dx}{dt} = f(x) - g(x) + \xi(t) . \quad (1)$$

The above Langevin equation is based on a continuous description of molecular species: time evolution of an input or output concentrations x produced at a rate $f(x)$ and degraded at rate $g(x)$ defines a deterministic flux of reacting species and can be used when modelling processes involve sufficient concentrations of reacting agents.

When, in turn, only a few molecules are present, discrete structure of single-reaction events becomes important and the evolution of the system is better described by an appro-

priate Master equation

$$P_i(t + \Delta t) = [f_{i-1}\Delta t + \mathcal{O}(\Delta t)]P_{i-1}(t) + [1 - (f_i + g_i)\Delta t + \mathcal{O}(\Delta t)]P_i(t) \\ + [g_{i+1}\Delta t + \mathcal{O}(\Delta t)]P_{i+1}(t),$$

where $P_i(t)$ is the probability for there being i molecules (objects) at time t , f_i is a probability per unit time of transition $i \rightarrow i + 1$ and g_i is a probability per unit time of the opposite transition $i \rightarrow i - 1$. Using (2) one can formulate the equation for the first moment $\langle i \rangle = \sum i P_i(t)$ and then apply a limiting procedure for converting it into a partial differential equation. The procedure involves introducing a small parameter ϵ and letting $x = \epsilon i$ and $P_i \equiv P(x, t|y, 0)$. Here $P(x, t|y, 0)$ is the probability that the random variable has the value x at time t given it had the value y at $t = 0$. By considering now a sequence of birth-and-death processes such that $\epsilon(f_i(\epsilon) - g_i(\epsilon)) = a(i\epsilon) + \mathcal{O}(\epsilon)$ and $\epsilon^2(f_i(\epsilon) + g_i(\epsilon)) = b(i\epsilon) + \mathcal{O}(\epsilon)$. Letting $\epsilon \rightarrow 0$ and using the above conditions, we arrive at the Fokker–Planck equation

$$\frac{\partial}{\partial t} P(x, t|y, 0) = -\frac{\partial}{\partial x} [a(x)P(x, t|y, 0)] + \frac{\partial^2}{\partial x^2} [b(x)P(x, t|y, 0)] . \quad (2)$$

We are usually interested in the effects of stochasticity for i not too small. Therefore, according to the above scheme, with increasing number of reactants, stochastic effects analysed via the ME (or FPE) are asymptotically equivalent to those described by the Langevin equation with a multiplicative noise term [15].

$$\frac{dx}{dt} = f(x) - g(x) + \sqrt{f(x) + g(x)}\xi_t = a(x) + \sqrt{b(x)}\xi_t \quad (3)$$

From amongst the presented possible ways of description of chemical and biological processes, we have chosen an approach using a chemical Langevin equation with an additive driving noise term as in Eq. (1) to demonstrate the positive role of both additive and multiplicative noises in a regulatory model of the catalytic reaction. The description of cancer growth kinetics is based on the phenomenological Michaelis–Menten scheme for the catalysis accompanying a spontaneous replication of cancer cells.

II. THE MODEL

The interaction between cancer cells and cytotoxic cells will be described by use of the predator-prey model based upon the Michaelis–Menten kinetic scheme [4, 14, 16, 17, 18, 19].

This model is a classical one and has been extensively studied since the 1970s. Its validity has been verified experimentally e.g. in [16], where the authors examined the mechanism of immune rejection of a tumour induced by Moloney murine sarcoma virus. The behavior of the cellular populations may be represented by the following scheme:



X represents here the population of tumour cells. Y , Z and P are populations of active cytotoxic cells, bound cells and dead tumour cells, respectively. Cytotoxic cells bind the tumour cells at rate k_1 ; subsequently, the cancer cells which have been bound are killed and the complex dissociates at rate k_2 ; finally, dead cancer cells decay at a rate k_3 . The mechanism of cell replication will be first presented in one-dimensional case: Cancer cells replicate at a rate λ , but the process is being inhibited due to a limited volume of a compartment, whose maximal carrying capacity is denoted by N . We divide a one-dimensional space into small compartments of size $\Delta r = Na$, where a is a typical cell diameter. The overflow of replicated cells may diffuse to neighbouring compartments at a rate proportional to the volume available there. If X_i is the number of cancer cells occupying the i th compartment at time t , then, after a discrete time step Δt :

$$\begin{aligned} X_i(t + \Delta t) = & X_i + \lambda \Delta t X_i \left(\frac{N - X_i - P_i}{N} \right) \\ & + \lambda \Delta t \left(X_{i-1} \frac{N - X_i - P_i}{N} + X_{i+1} \frac{N - X_i - P_i}{N} \right. \\ & \left. - X_i \frac{N - X_{i-1} - P_{i-1}}{N} - X_i \frac{N - X_{i+1} - P_{i+1}}{N} \right). \end{aligned} \quad (5)$$

An analogous formula can be written for a two-dimensional case. The conversion of such an equation into a continuous form will yield a logistic term (saturating growth) and diffusion terms. Additionally, we assume that immune cells can diffuse at a rate proportional to a coefficient D . External environmental fluctuations will be modelled by the additive Gaussian noise $\xi(\vec{r}, t)$ with autocorrelation $\langle \xi(\vec{r}, t) \xi(\vec{r}', t') \rangle = \delta(t - t') \delta(\vec{r} - \vec{r}')$. We assume that since $\xi(\vec{r}, t)$ is an environmental noise (modelling e.g. local temperature changes), it acts in the same way on all system variables. Fluctuations in immune response will be introduced as a multiplicative dichotomous Markovian noise $\eta(t) = \pm \Delta$ with mean frequency γ and autocorrelation $\langle \eta(t) \eta(t') \rangle = \frac{\Delta^2}{2} e^{-2\gamma|t-t'|}$. The spatio-temporal evolution of the tumour

due to the above processes will be then described by a set of balance equations with stochastic components:

$$\begin{cases} \frac{\partial x}{\partial t} = \lambda[1 - (x + p)]x - (k_1 + \eta(t))yx + \\ \quad + \lambda(1 - p)(Na)^2 \nabla^2 x + \lambda x(Na)^2 \nabla^2 p + \sigma \xi(\vec{r}, t) \\ \frac{\partial y}{\partial t} = -(k_1 + \eta(t))yx + k_2 z + D \nabla^2 y + \sigma \xi(\vec{r}, t) \\ \frac{\partial z}{\partial t} = (k_1 + \eta(t))yx - k_2 z + \sigma \xi(\vec{r}, t) \\ \frac{\partial p}{\partial t} = k_2 z - k_3 p + \sigma \xi(\vec{r}, t) . \end{cases} \quad (6)$$

The $x(\vec{r}, t)$, $y(\vec{r}, t)$, $z(\vec{r}, t)$ and $p(\vec{r}, t)$ are local densities of cells at point \vec{r} . We assume that the noise intensity σ is the same for each variable of the system. Both noises are assumed to be statistically independent: $\langle \xi(\vec{r}, t) \eta(s) \rangle = 0$.

III. STABILITY ANALYSIS

The stationary points $\{x^*, y^*, z^*, p^*\}$ of the system are given by:

$$\{0, y, 0, 0\} \quad (7)$$

and

$$\left\{ \frac{k_3}{\lambda} \frac{\lambda - k_1 y}{k_3 + k_1 y}, y, \frac{k_1 k_3 y}{\lambda k_2} \frac{\lambda - k_1 y}{k_3 + k_1 y}, \frac{k_1 y}{\lambda} \frac{\lambda - k_1 y}{k_3 + k_1 y} \right\}, \quad (8)$$

where the value of y is defined by the condition $y(t) + z(t) = \text{const.} = E$. The sets of stationary points form two branches in the x - y - z - p -space. The branch (7) changes its stability at the point $\{0, \frac{\lambda}{k_1}, 0, 0\}$. It is repelling for $0 < y < \frac{\lambda}{k_1}$ and attracting for $\frac{\lambda}{k_1} < y < 1$. The branch (8) is attracting for $0 < y < \frac{k_3}{k_1} \left(-1 + \sqrt{1 + \frac{\lambda}{k_1}} \right)$. For $\frac{k_3}{k_1} \left(-1 + \sqrt{1 + \frac{\lambda}{k_1}} \right) < y < 1$ it consists of saddle points [10]. When E, k_2, k_3 are fixed, stability properties of the system depend on the k_1 parameter (connected with the immune response efficiency) which is controlled by the dichotomous noise. As the value $k_1 + \eta(t)$ changes, the branch (8) moves up and down [10].

IV. SIMULATION

We have solved the stochastic differential equations (6) numerically, using their discrete form analogous to (5) (i.e. the Euler scheme), on a 128×128 square lattice with periodic

boundary conditions for \vec{r} . According to the statistical properties of $\eta(t)$, the waiting time between two switchings was generated from the exponential distribution. Since x, y, z and p are densities, their values never can be greater than 1 or less than 0. Consequently, we applied reflecting boundaries at those values.

We performed a simulation with the following values of parameters:

$$\begin{aligned} \lambda &= 0.5, \quad Na = 1, \quad D = 0.05, \quad \sigma = 0.01, \quad \Delta = 0.5, \\ k_1 &= 1.75, \quad k_2 = 0.1, \quad k_3 = 0.1, \quad \gamma = 0.01. \end{aligned} \tag{9}$$

γ is the mean rate of switching in $\eta(t)$. Simulation time: $T = 20000$. Initial conditions:

$$x(\vec{r}, 0) = 0, \quad y(\vec{r}, 0) = 0.4, \quad z(\vec{r}, 0) = 0, \quad p(\vec{r}, 0) = 0. \tag{10}$$

The values of parameters and initial conditions have been chosen so that we could obtain a distinct spatial pattern: The immune response rates $k_1 + \Delta$ and $k_1 - \Delta$, along with λ lead to two different types of stationary behaviour (see Sec. V). The mean switching rate is one or two orders of magnitude slower than other kinetic parameters, which gives the system a possibility to approach the stationary states. The environmental noise intensity σ has been chosen in such a way that, combined with $\eta(t)$, it allows the system to jump between both mentioned states. The noise is, however, weak enough to let the system form a pattern (otherwise the Gaussian noise would dominate the picture) [20]. At the selected value of D , the pattern has sufficiently distinct boundaries and is relatively stable (at higher values of D it would dissolve quickly, whereas at smaller D it would form small “grains”). Values of parameters k_2 and k_3 have been chosen by a trial-and-error procedure: k_2 is responsible for the dissociation of z into $y + p$. If the dissociation rate is large, then the active immune cells y are being released faster and thus the immune response is more effective. The k_3 parameter determines the rate at which dead cancer cells are eliminated. Since dead cells occupy the living space, this parameter controls the effective replication rate of cancer cells.

V. RESULTS

The system driven by the additive Gaussian noise in the absence of the dichotomous switching ($\eta(t) = \text{const} = +\Delta$ or $\eta(t) = \text{const} = -\Delta$) fluctuates in the neighbourhood of one of the two attracting branches, without jumping between them [10]. When the dichotomous

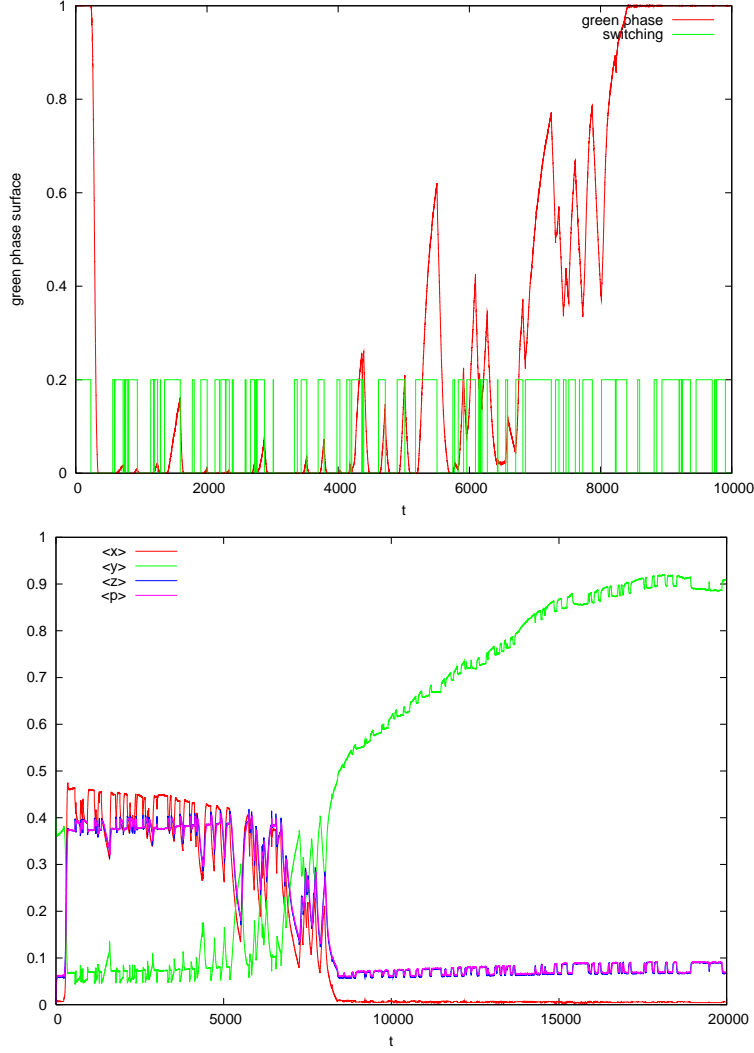


FIG. 1: Left: Total area of the “ y -phase” (counted points on the lattice where x is smaller than 0.03). Right: Average densities of x , y and z populations over the simulation area.

noise is present, a coexistence of the two “phases” is possible. Some parts of the system (the “ x -phase”) can fluctuate around the lower branch, whereas other parts (the “ y -phase”) fluctuate in the vicinity of the upper one. We observe the emergence of clusters, where immune cells y , or, respectively, cancer cells x predominate. The phase boundaries move back and forth depending on the dichotomous changes in the immune response intensity [10]. We observe several episodes of sudden formation and decay of “ y -phase” clusters (Fig. 1) until the “ y -phase” prevails globally (Fig. 1).

VI. CONCLUSIONS

The measurement of the “ y -phase” total area and the average population densities over the simulation area (Fig.1) allow to notice that the spatially extended system, as a whole, possesses two stationary states. We can observe the transition between them: Shortly after starting from $x = 0$, $y = 0.4$, $z = 0$, $p = 0$, the system falls down onto the “ x -phase” branch. The average population densities fluctuate around a certain constant level (the first stationary state). After some time, clusters of “ y -phase” begin to emerge and disappear, which is caused by the dichotomous changes in the position of the stationary branch (8). The average population level of x , y , z and p fluctuates strongly. As time goes on, clusters form more and more frequently whereas their area becomes larger and larger. Finally, the whole system escapes onto the “ y -phase” branch and climbs up [10] towards a new stationary state (fluctuations between reflecting boundaries of $x = 0$, $y = 1$, $z = 0$), in which the average population densities approach a new constant level, about which they weakly fluctuate (the second stationary state).

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